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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,466	09/19/2006	Mariusz W. Szkudlinski	TROP-001/01US 304828-2046	9091

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EXAMINER	
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ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,466	SZKUDLINSKI ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40,43-67,84-99,102-115,118-129,132,133 and 136-138* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2006* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-6,11,12,15,26-28,40,43-46,52,58,67,84-93,95,97-99,102-109,111,113-115,118-123,127-129, 132-133 and 136-138.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 7-10,13,14,16-25,29-39,47-51,53-57,59-66,68-83,94,96,102-103,110,112,118-119,124-126 and 132-133.

Continuation of Disposition of Claims: Claims rejected are 1-6,11,12,15,26-28,40,43-46,52,58,67,84-93,95,97-99,104-109,111,113-115,120-123,127-129 and 136-138.

DETAILED ACTION

Response to Amendment

Applicant's amendment filed 28 June 2010 is acknowledged. Claims 1, 4, 6, 43, 46, 84, 104, 120, 123 are amended. Claims 41, 42, 68-83, 100, 101, 116, 117, 130, 131, 134 and 135 are cancelled. Claim 138 is new. Claims 7, 8, 9, 10, 13, 14, 16-25, 29-39, 47-51, 53-57, 59-66, 94, 96, 102-103, 110, 112, 118-119, 124-126, 132, and 133 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b).

Claims 1-6, 11, 12, 15, 26-28, 40, 43-46, 52, 58, 67, 84-93, 95, 97-99, 104-109, 111, 113-115, 120-123, 127-129 and 136-138 are under examination.

Formal Matters

In response to Applicants amendment of the claims, all of the previous rejections of record are hereby withdrawn. However, upon reconsideration of the claims and the art, new rejections are made below. This Office action is made non-final, to give Applicants the opportunity to respond to the new rejections.

Claim Objections Withdrawn

The objection to claim 42 for minor informalities 42 is withdrawn in response to Applicants' cancellation of that claim.

The objection to claims 84, 107 and 108 for minor informalities is withdrawn in response to Applicants' deletion of "□" and replacement with "α".

New Objections/Rejections

Claim Objections

Claims 1, 37, and 38 are objected to because of the following informalities:

The objection to claim 1 because in line 6 the "a" in the phrase "a ten fold" is awkward grammatically is maintained. It is suggested that the claim recite "at least about ten fold".

Claim 137 is objected to because it comma has a period at the end of the claim instead of the required period.

Claim 138 is objected to because it recites "FSG" in line 2 of the claim and should be amended to recite "FSH".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 11, 12, 15, 26-28, 40, 43-46, 52, 58, 67 and 109 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "FSH comprising a modified α-subunit and a modified β-subunit, wherein the modified subunit", which is unclear, because it is not clear whether "the

modified subunit" and the amino acid mutations that follow are referring back to the α- or the β-subunit. Note that amending the phrase to recite "FSH comprising a modified α-subunit and a modified β-subunit, wherein the modified β-subunit" would overcome this rejection. Claims 2-6, 11, 12, 15, 26-28, 40, 43-46, 52, 58 and 67 are rejected for depending upon an indefinite claim.

Claim 12 is rejected as being indefinite because the claim recites "wherein said basic amino acids of the α-subunit are P16R and Q20R". However P16R and Q20R are not "amino acids", but rather they represent specific amino acid substitutions. It is noted that this issue could be overcome by amending the claim to recite, for example, "The modified FSH of claim 11, wherein said basic amino acids at positions 16 and 20 are substituted with an arginine".

Claim 28 is rejected as being indefinite because the claim recites "wherein said basic amino acids of the α-subunit are Q13R, E14R, P16R and Q20R". However, Q13R, E14R, P16R and Q20R are not "amino acids", but rather they represent specific amino acid substitutions. It is noted that this issue could be overcome by amending the claim to recite, for example, "The modified FSH of claim 27, wherein said basic amino acids at positions 13, 14, 16 and 20 are substituted with an arginine".

Claim 43 is rejected as being indefinite because the claim recites "wherein said basic amino acids of the α-subunit is E4R". However E4R is not an "amino acid", but rather represents a specific amino acid substitution. It is noted that this issue could be overcome by amending the claim to recite, for example, "The modified FSH of claim 1, wherein said basic amino acid at position 4 is substituted with an arginine".

Claims 44-46 are indefinite because claim 44 recites, "A nucleic acid encoding the modified FSH α-subunit of claim 1," but claim 1 has been amended to recite, "and a modified β-subunit..." It is not clear whether claim 44 only meant to encode half of the recited modified FSH, and if so, then it is not clear how claim 44 and its dependents, 45 and 46, limit claim 1 as amended.

Claim 109 is indefinite because it is not clear whether the phrase "contains an arginine at positions 13, 14, 16 and 20 refers to the α-subunit, β-subunit or both since claim 104 has been amended to recite a modified β-subunit in addition to the α-subunit. Note claim 123, which was amended to recite "of the α-subunit." Such an amendment at the end of claim 109 would overcome this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 11, 12, 15, 26-28, 40, 43-46, 52, 58, 67, 84-93, 95, 97-99, 104-109, 111, 113-115, 120-123, 127-129 and 136-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Szkudlinski et al. (WO97/42322, US HEALTH published 13 November 1997) or Szkudlinski et al. (U.S. Patent Publication 2002/0110909, published 15 August 2002) and further in view of Schambye et al., (Patent Publication No. 2002/0127652, published 12 September 2002). All references are of record. The amended claims are drawn to a modified follicle stimulating hormone or FSH superagonist having increased half-life and activity compared to wild-type FSH and having two or three basic amino acid substitutions selected from the group consisting of positions 13, 14, 16, 17, 20, 21, 22, 66, 68, 73, 74 and 81 the SEQ ID NO: 1 (i.e., the α-subunit of FSH), wherein said basic amino acid is arginine, lysine or histadine; nucleic acids encoding said superagonists, as well as vectors and host cells suitable for expressing said nucleic acids; methods of treating infertility and improving oocyte quality

in animals. Additionally, the amended claims are drawn to the FSH superagonist having at least one basic amino acid substitution selected from the group consisting of residues 2, 4, 14, 63, 64, 67, 69 of SEQ ID NO: 2 (i.e., the β-subunit of FSH), wherein said basic substitution is arginine. In addition, claims 52 and 58 are drawn to increasing half life and the addition of polyethylene glycol (PEG), respectively. The first issue is to consider when making a rejection under 35 U.S.C. 103(a) is to determine the scope and contents of the prior art.

(i) **Szkudlinski:** The WO97/42322 document teaches a modified glycoprotein hormone wherein there are three or four basic amino acid substitutions selected from the group consisting of positions 11, 13, 14, 16, 17 and 20 of the α-subunit of FSH (see, for example, pages 3, 6, whole pages; p. 8, lines 19-30; p. 17, lines 6-29; p. 18, lines 1-18; p. 19, lines 5-16; claims 1-11, 18, 22). The α-subunit of the WO document corresponds to SEQ ID NO: 1 of the instant case. The WO97/42322 document teaches two to five basic amino acid substitutions selected from the group consisting of amino acids 13, 14, 16, 17 and 20, which falls squarely into the range recited in the claims. Further, basic substitutions specifically at residues 16 and 20 of the α-subunit are taught at p. 17, line 30 of the WO97/42322 document (claim 11); basic substitutions specifically at residues 13, 14, 16 and 20 are taught at p. 19, line 13 and claims 5 and 18. Basic amino acids are selected from the group lysine, arginine and histidine (see p. 9, line 1; p. 18, line 18; p. 19, lines 16 and 26-27 and claim 22 of the WO97/42322 document). Note that claims 1 and 2 of the WO97/42322 document recite:

1. A human glycoprotein hormone comprising at least three basic amino acids in the α-subunit at positions selected from the group consisting of positions 11, 13, 14,

16, 17, and 20.
2. The human glycoprotein hormone of claim 1, further comprising a fourth basic amino acid at a position selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.

Claim 5 of the WO97/42322 document recites:

The human glycoprotein hormone of claim 2, wherein basic amino acids are at positions 13, 14, 16, and 20.

Further note that claim 18 of the WO97/42322 document recites:

The glycoprotein hormone of any of claims 1 - 11, wherein the hormone is follicle-stimulating hormone.

And finally, that claim 22 of the WO97/42322 document recites:

The human glycoprotein hormone any of claims 1 - 20, wherein the basic amino acids are selected from the group consisting of lysine and arginine.

Thus, the WO97/42322 document clearly teaches an FSH variant with arginine substitutions at residues 13, 14, 16 and 20 of the α-subunit.

The WO97/42322 document teaches recombinant methods of making proteins, suitable hosts and vectors therefor. Since instant claims 44-46 only recite nucleic acids, host and vectors encoding the α-subunit, all of the limitations of those claims are met by the Szkudlinski documents. Further, it is taught in the WO97/42322 document that the contemplated modified glycoprotein hormones have increased activity, for example at pages 22 and 23. Finally, the WO97/42322 document also teaches methods of assisted reproduction, for example, at p. 24, lines 25-30 and p. 26, lines 4-12. Injection is contemplated at p. 25, line 20. The method claims in the instant specification recite methods of administering an effective amount of FSH superagonist containing basic amino acid substitutions at one or more positions selected from 13, 14, 16 and 20 to

improve the quality of oocytes in a human or an animal (claims 84-92, 95, 97-99); to induce superovulation (claims 104-108, 111, 113-115); to enhance superovulation (claims 120-122, 127-129). As noted above, U.S. Patent Publication, 2002/0110909, is a related document and the corresponding citations anticipating the claims are found at claims 1, 2, 5, 18, 25, 27 and 29; paragraphs [0004], [0006], [0031]-[0041]; [0045], [0050], [0051], [0053]-[0055], [0073], [0074].

The second issue is to ascertain the differences between the prior art and the instant claims. Neither of the Szkudlinski documents teach modifications of the FSH β-subunit (i.e., SEQ ID NO: 2) at positions 2, 4, 14, 63, 64, 67 and 69 nor do they specifically mention PEGylation of the FSH variants.

(ii) **Schambye**: Schambye et al. teach a modified FSH having the introduction of a basic amino acid (i.e., a lysine residue) in the α-subunit, and also teaches the introduction of a lysine residue into the β-subunit, for example, residues 2, 4, 64, 67, and 69 (see paragraphs [0115]-[0116]). Schambye teaches a list of conservative amino acid substitutions at paragraph [0044] that includes both arginine and lysine. Further, at paragraphs [0113] – [0120], Schambye suggest multiple possible residues in both the α- and β-subunits, including all of the residues recited in claim 6 (i.e., the α-subunit or SEQ ID NO: 1—paragraph [0015] of Schambye) and residues 2, 67 and 69 of the β-subunit (i.e., SEQ ID NO: 2—paragraph [0116] of Schambye). Finally, at paragraph [0120], Schambye suggest that particularly arginine is an appropriate substitute for lysine in the contemplated amino acid positions. Further, Schambye teach a method of constructing superactive analogs of human glycoprotein hormones comprising comparing the amino

acid sequence of a more active homolog from another species to the human glycoprotein hormone and substituting amino acids in the human glycoprotein hormone with the corresponding amino acids from the homolog of the other species and selecting those superactive analogs with the most activity (see for instance, claim 79 of Schambye; paragraphs [0012]; [0025]; [0077] and [0078]). Recombinant methods of protein expression are contemplated at paragraphs [0179]-[0180]. In addition, Schambye et al. contemplate human FSH at paragraph [0057]. Schambye et al. teach at paragraph [0137] the addition of PEG in order to increase functional in vivo half-life and/or serum half-life.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the FSH alpha subunit teachings of Szkudlinski by combining the α-subunit with the FSH β-subunit as taught by Schambye. It also would have been obvious to substitute arginine residues in positions 2, 4, 64, 67, and 69 of the β-subunit of Schambye.

(iii) First, it would have been obvious to combine the α-subunits of Szkudlinski with the β-subunits of Schambye because Schambye teach a method of constructing superactive analogs of human glycoprotein hormones comprising comparing the amino acid sequence of a more active homolog from another species to the human glycoprotein hormone and substituting amino acids in the human glycoprotein hormone with the corresponding amino acids from the homolog of the other species and selecting those superactive analogs with the most activity (see for instance, claim 79 of Schambye; paragraphs [0012]; [0025]; [0077] and [0078]). Based upon this teaching

the person of ordinary skill in the art would extrapolate that the superactive analogs generated in Skzudlinski by the α-subunit substitutions taught therein would serve as a suitable template for building a "superactive analog" as taught in Schambye. Namely, based upon the teachings of Schambye, which suggest using other substitutions from other highly active analogs in order to build a "superactive analog", one of ordinary skill in the art would be motivated to construct a superactive analog by combining the α-subunits of Szkudlinski to the β-subunits of Schambye.

(iv) Second, it would have been obvious to substitute arginine residues in positions 2, 4, 64, 67 and 69 of the β-subunit of Schambye. The motivation for utilizing arginine residues at specific positions in the FSH beta subunit is suggested by both the Szkudlinksi and Schambye documents. For instance, lysine and arginine are both basic amino acids, and this is evidenced by Szkudlinski suggesting either amino acid as a suitable substitution of the α-subunit residues. Further, Schambye teaches a list of conservative amino acid substitutions at paragraph [0044] that includes both arginine and lysine. Further, at paragraphs [0113] – [0120], Schambye suggest multiple possible residues in both the α- and β-subunits, including all of the residues recited in claim 6 (i.e., the α-subunit or SEQ ID NO: 1—paragraph [0015] of Schambye) and residues 2, 67 and 69 of the β-subunit (i.e., SEQ ID NO: 2—paragraph [0116] of Schambye). Finally, at paragraph [0120], Schambye suggest that particularly arginine is an appropriate substitute for lysine in the contemplated amino acid positions. Regarding the interchangeability of arginine and lysine, the person of ordinary skill in the art would recognize the simple substitution of one known element, namely a basic amino acid

arginine for another, a basic amino acid, lysine, to obtain predictable results. The prior art suggests that in choosing between arginine and lysine, one of ordinary skill in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. The level of skill in the prior art is high with respect to FSH variants and the substitution of basic amino acids such as lysine and arginine.

(v) Regarding the PEGylation of the FSH superagonists, it would have been obvious to do so because Schambye et al. teach that PEG is suitable for reducing immunogenicity and/or increasing functional in vivo half-life and/or serum half-life. The person of ordinary skill in the art would have been motivated to make the modification because, as taught in Schambye et al., PEGylation results in a need for fewer injections (for instance, see paragraph [0196] of Schambye et al.). Furthermore, the person of ordinary skill in the art could have reasonably expected success because PEGylation is old in the art, and well understood to be effective at reducing immunogenicity and increasing half-life. Thus the claims do not contribute anything non-obvious over the prior art. The level of skill in the prior art is high with respect to PEGylation of polypeptides.

The final factor that one must consider is objective evidence present in the application indicating obviousness. There is no specific evidence present in the instant application of surprising or unexpected regarding the substitution of arginine over lysine. Further, the prior art of Schambye et al. already suggested using other substitutions from other highly active analogs in order to build a "superactive analog", thus one of ordinary skill in the art would be guided to construct a superactive analog by combining

the α-subunits of Szkudlinski with the β-subunits of Schambye. Finally, the prior art (Schambye) already taught that PEGylation is suitable for reducing immunogenicity and/or increasing functional in vivo half-life and/or serum half-life. In summary, the combined teachings of Szkudlinski and Schambye suggest the claimed modified FSH superagonists. Therefore it follows that the FSH variants described therein would also have superagonist properties (increased absorption, binding affinity, half-life, positively charged at neutral pH) since the prior art suggests equivalent substitutions. Further, the claims recite "at least about" regarding the fold increase in potency, thus this limitation is broad and encompasses even minor increases in potency.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 11, 12, 15, 26-28, 40, 43-46, 52, 58, 67 and 136-138 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-45 of U.S. Patent No. 7,070,788 in view of Schambye et al (cited above). Although the conflicting claims are not identical, they are not patentably distinct from each other because in both cases, the claims are drawn to modified human FSH having basic amino acid (i.e., lysine or arginine) substitutions at positions 11, 13, 14, 16, 17 and 20 of the α-subunit, nucleic acids, vectors and host cells for expressing said FSH variants. The difference between the claim sets lies in the fact that the amended claims of the instant application recite specific residues for the modified β-subunit and that the modified FSH is PEGylated. Nevertheless, Schambye et al. teach a modified FSH having the introduction of a basic amino acid (i.e., a lysine residue) in the α-subunit, and also teaches the introduction of a lysine residue into the β-subunit, for example, residues 2, 4, 64, 67, and 69 (see paragraphs [0115]-[0116]). Recombinant methods of protein expression are contemplated at paragraphs [0179]-[0180]. In addition, Schambye et al. contemplate human FSH at paragraph [0057]. Schambye et al. teach at paragraph [0137] the addition of PEG in order to increase functional in vivo half-life and/or serum half-life.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the beta subunit of the FSH molecule of the '788 patent by substituting arginine residues in positions 2, 4, 64, 67, and 69 of the β-subunit. Schambye teaches a list of conservative amino acid substitutions at paragraph [0044] that includes both arginine and lysine. Further, at paragraphs [0113] – [0120],

Schambye suggest multiple possible residues in both the α- and β-subunits, including all of the residues recited in claim 6 (i.e., the α-subunit or SEQ ID NO: 1—paragraph [0015] of Schambye) and residues 2, 67 and 69 of the β-subunit (i.e., SEQ ID NO: 2—paragraph [0116] of Schambye). Finally, at paragraph [0120], Schambye suggest that particularly arginine is an appropriate substitute for lysine in the contemplated amino acid positions. Regarding the interchangeability of arginine and lysine, the person of ordinary skill in the art would recognize the simple substitution of one known element, namely a basic amino acid arginine for another, a basic amino acid, lysine, to obtain predictable results. Schambye suggests that in choosing between arginine and lysine, one of ordinary skill in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. The level of skill in the prior art is high with respect to FSH variants and the substitution of basic amino acids such as lysine and arginine.

Regarding the PEGylation of the FSH subunits, it would have been obvious to do so because Schambye et al. teach that PEG is suitable for reducing immunogenicity and/or increasing functional in vivo half-life and/or serum half-life. The person of ordinary skill in the art would have been motivated to make the modification because, as taught in Schambye et al., PEGylation results in a need for fewer injections (for instance, see paragraph [0196] of Schambye et al.). Furthermore, the person of ordinary skill in the art could have reasonably expected success because PEGylation is old in the art, and well understood to be effective at reducing immunogenicity and increasing half-life.

Finally, the claims of the '788 patent do not teach increased potency, absorption or binding affinity, nevertheless, since the '788 patent teaches the same FSH α-subunit modifications, it follows that the FSH variants described therein would also have superagonist properties (increased absorption, binding affinity, half-life, positively charged at neutral pH) since the prior art suggests equivalent substitutions. Further, the instant claims recite "at least about" regarding the fold increase in potency, thus this limitation is broad and encompasses even minor increases in potency.

Conclusion

Claims 1-6, 11, 12, 15, 26-28, 40, 43-46, 52, 58, 67, 84-93, 95, 97-99, 104-109, 111, 113-115, 120-123, 127-129 and 136-138 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 9:00am - 3:00pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest

/Bridget E Bunner/
Primary Examiner, Art Unit 1647